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## DEPARTMENT OF HEALTH AND HUMAN SERVICES

### Food and Drug Administration

#### 21 CFR Part 178

[Docket No. 95F-0150]

### Indirect Food Additives: Adjuvants, Production Aids, and Sanitizers

**AGENCY:** Food and Drug Administration, HHS.

**ACTION:** Final rule.

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**SUMMARY:** The Food and Drug Administration (FDA) is amending the food additive regulations to provide for the safe use of 7-oxa-3,20-diazadispiro-[5.1.11.2]-heneicosan-21-one, 2,2,4,4-tetramethyl-, hydrochloride, reaction products with epichlorohydrin, hydrolyzed, polymerized (CAS Reg. No. 202483-55-4) as an antioxidant and/or stabilizer for polyolefins intended for contact with food. This action is in response to a petition filed by Hoechst Aktiengesellschaft.

**DATES:** The regulation is effective (*insert date of publication in the Federal Register*). Submit written objections and requests for a hearing by (*insert date 30 days after date of publication in the Federal Register*).

**ADDRESSES:** Submit written objections to the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

**FOR FURTHER INFORMATION CONTACT:** Vivian M. Gilliam, Center for Food Safety and Applied Nutrition (HFS-215), Food and Drug Administration, 200 C St. SW., Washington, DC 20204, 202-418-3094.

**SUPPLEMENTARY INFORMATION:**

cf 98238

NFR 1

## I. Background

In a notice published in the **Federal Register** of July 12, 1995 (60 FR 35914), FDA announced that a food additive petition (FAP 5B4461) had been filed by Hoechst Aktiengesellschaft, c/o 1001 G St. NW., suite 500 West, Washington, DC 20001. The petition proposed that the food additive regulations in § 178.2010 *Antioxidants and/or stabilizers for polymers* (21 CFR 178.2010) be amended to provide for the safe use of polymeric 2,2,4,4-tetramethyl-7-oxa-3,20-diaza-20-(2,3-epoxypropyl)-dispiro-[5.1.11.2]-heneicosane-21-one (CAS Reg. No. 78301-43-6) as an antioxidant and/or stabilizer for polyolefins intended for contact with food.

Subsequent to the filing of the petition, Hoechst Aktiengesellschaft sold its speciality business, including food additive petition 5B4461, to Clariant AG, Switzerland. The petitioner also obtained a new Chemical Abstracts Service (CAS) Registry number for the additive under the following name: 7-oxa-3,20-diazadispiro-[5.1.11.2]-heneicosan-21-one, 2,2,4,4-tetramethyl-, hydrochloride, reaction products with epichlorohydrin, hydrolyzed, polymerized (CAS Reg. No. 202483-55-4).

In FDA's evaluation of the safety of 7-oxa-3,20-diazadispiro-[5.1.11.2]-heneicosan-21-one, 2,2,4,4-tetramethyl-, hydrochloride, reaction products with epichlorohydrin, hydrolyzed, polymerized the agency reviewed the safety of the additive itself and the chemical impurities that may be present in the additive resulting from its manufacturing process. Although the additive itself has not been shown to cause cancer, it has been found to contain minute amounts of epichlorohydrin, a carcinogenic impurity resulting from the manufacture of the additive. Residual amounts of impurities are commonly found as constituents of chemical products, including food additives.

## II. Determination of Safety

Under the general safety standard of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 348(c)(3)(A)), a food additive cannot be approved for a particular use unless a fair evaluation of the data available to FDA establishes that the additive is safe for that use. FDA's

food additive regulations (21 CFR 170.3(i)) define safe as “a reasonable certainty in the minds of competent scientists that the substance is not harmful under the intended conditions of use.”

The food additives anticancer, or Delaney, clause of the act (21 U.S.C. 348(c)(3)(A)) provides that no food additive shall be deemed safe if it is found to induce cancer when ingested by man or animal. Importantly, however, the Delaney clause applies to the additive itself and not to impurities in the additive. That is, where an additive itself has not been shown to cause cancer, but contains a carcinogenic impurity, the additive is properly evaluated under the general safety standard using risk assessment procedures to determine whether there is a reasonable certainty that no harm will result from the intended use of the additive. *Scott v. FDA*, 728 F.2d 322 (6th Cir. 1984).

### **III. Safety of the Petitioned Use of the Additive**

FDA estimates that the petitioned use of the additive, 7-oxa-3,20-diazadispiro-[5.1.11.2]-heneicosan-2 1-one,2,2,4,4-tetramethyl-,hydrochloride, reaction products with epichlorohydrin, hydrolyzed, polymerized, will result in exposure to no greater than 224 parts per billion (ppb) of the additive in the daily diet (3 kilogram (kg)) or an estimated daily intake of 0.67 milligram per person per day (mg/p/d) (Ref.1).

FDA does not ordinarily consider chronic toxicological studies to be necessary to determine the safety of an additive whose use will result in such low exposure levels (Ref. 2), and the agency has not required such testing here. However, the agency has reviewed the available toxicological data on the additive and concludes that the estimated small dietary exposure resulting from the petitioned use of this additive is safe.

FDA has evaluated the safety of this additive under the general safety standard, considering all available data and using risk assessment procedures to estimate the upper-bound limit of lifetime human risk presented by epichlorohydrin, the carcinogenic chemical that may be present as an impurity in the additive. The risk evaluation of epichlorohydrin has two aspects: (1) Assessment

of exposure to the impurity from the petitioned use of the additive, and (2) extrapolation of the risk observed in the animal bioassays to the conditions of exposure to humans.

#### *A. Epichlorohydrin*

FDA has estimated the exposure to epichlorohydrin from the petitioned use of the additive as an antioxidant and/or stabilizer for polyolefins to be no more than 0.011 ppb in the daily diet (3 kg) or 33 nanograms (ng)/p/d (Ref.1). The agency used data from a carcinogenesis bioassay on epichlorohydrin conducted by Konishi et al. (Ref. 4), to estimate the upper-bound limit of lifetime human risk from exposure to this chemical resulting from the petitioned use of the additive. The authors reported that the test material caused significantly increased incidence of stomach papillomas and carcinomas in male rats.

Based on the agency's estimate that exposure to epichlorohydrin will not exceed 33 ng/p/d, FDA estimates that the upper-bound limit of lifetime human risk from the petitioned use of the subject additive is  $1.5 \times 10^{-9}$  or 1.5 in a billion (Ref. 3). Because of the numerous conservative assumptions used in calculating the exposure estimate, the actual lifetime-averaged individual exposure to epichlorohydrin is likely to be substantially less than the estimated exposure, and therefore, the probable lifetime human risk would be less than the upper-bound limit of lifetime human risk. Thus, the agency concludes that there is reasonable certainty that no harm from exposure to epichlorohydrin would result from the petitioned use of the additive.

#### *B. Need for Specifications*

The agency has also considered whether specifications are necessary to control the amount of epichlorohydrin as an impurity in the additive. The agency finds that specifications are not necessary for the following reasons: (1) Because of the low level at which epichlorohydrin may be expected to remain as an impurity following production of the additive, the agency would not expect this impurity to become a component of food at other than extremely low levels; and (2)

the upper-bound limit of lifetime human risk from exposure to epichlorohydrin is very low, 1.5 in a billion.

#### **IV. Conclusion**

FDA has evaluated data in the petition and other relevant material. Based on this information, the agency concludes that the proposed use of the additive as an antioxidant and/or stabilizer for polyolefins intended for contact with food is safe, and that the additive will achieve its intended technical effect. Therefore, the agency concludes that the regulations in § 178.2010 should be amended as set forth below.

In accordance with § 171.1(h) (21 CFR 171.1(h)), the petition and the documents that FDA considered and relied upon in reaching its decision to approve the petition are available for inspection at the Center for Food Safety and Applied Nutrition by appointment with the information contact person listed above. As provided in § 17 1.1 (h), the agency will delete from the documents any materials that are not available for public disclosure before making the documents available for inspection,

#### **V. Paperwork Reduction Act of 1995**

This final rule contains no collection of information. Therefore clearance by the Office of Management and Budget under the Paperwork Reduction Act of 1995 is not required.

#### **VI. Environmental Impact**

The agency has carefully considered the potential environmental effects of this action. FDA has concluded that the action will not have a significant impact on the human environment, and that an environmental impact statement is not required. The agency's finding of no significant impact and the evidence supporting that finding, contained in an environmental assessment, may be seen in the Dockets Management Branch (address above) between 9 a.m. and 4 p.m., Monday through Friday.

## VII. Objections

Any person who will be adversely affected by this regulation may at any time on or before *(insert date 30 days after date of publication in the **Federal Register**)*, file with the Dockets Management Branch (address above) written objections thereto. Each objection shall be separately numbered, and each numbered objection shall specify with particularity the provisions of the regulation to which objection is made and the grounds for the objection. Each numbered objection on which a hearing is requested shall specifically so state. Failure to request a hearing for any particular objection shall constitute a waiver of the right to a hearing on that objection. Each numbered objection for which a hearing is requested shall include a detailed description and analysis of the specific factual information intended to be presented in support of the objection in the event that a hearing is held. Failure to include such a description and analysis for any particular objection shall constitute a waiver of the right to a hearing on the objection. Three copies of all documents shall be submitted and shall be identified with the docket number found in brackets in the heading of this document. Any objections received in response to the regulation may be seen in the Dockets Management Branch between 9 a.m. and 4 p.m., Monday through Friday.

## VIII. References

The following references have been placed on display in the Dockets Management Branch (address above) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

1. Memorandum from A. B. Bailey, Chemistry and Environmental Review Team, to D. Harrison, Division of Petition Control, dated August 6, 1998.
2. Kokoski, C. J., "Regulatory Food Additive Toxicology," in Chemical Safety Regulation and Compliance, edited by F. Homburger, and J. K. Marquis, New York, NY, pp. 24-33, 1985.
3. Memo from Division of Petition Control (HFS-215) to Sara H. Henry, Quantitative Risk Assessment Committee (HFS-308), "Verification of upper bound risk calculation for epichlorohydrin (ECH) for petition No. FAP 5B4461," dated February 10, 1998.

4. Konishi, Y. et al., “Forestomach Tumors Induced by Orally Administered Epichlorohydrin in Male Wistar Rats,” *Gann*, 71:922–923, 1980.

### **List of Subjects in 21 CFR Part 178**

Food additives, Food packaging.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, 21 CFR part 178 is amended as follows:

### **PART 178—INDIRECT FOOD ADDITIVES: ADJUVANTS, PRODUCTION AIDS, AND SANITIZERS**

1. The authority citation for 21 CFR part 178 continues to read as follows:

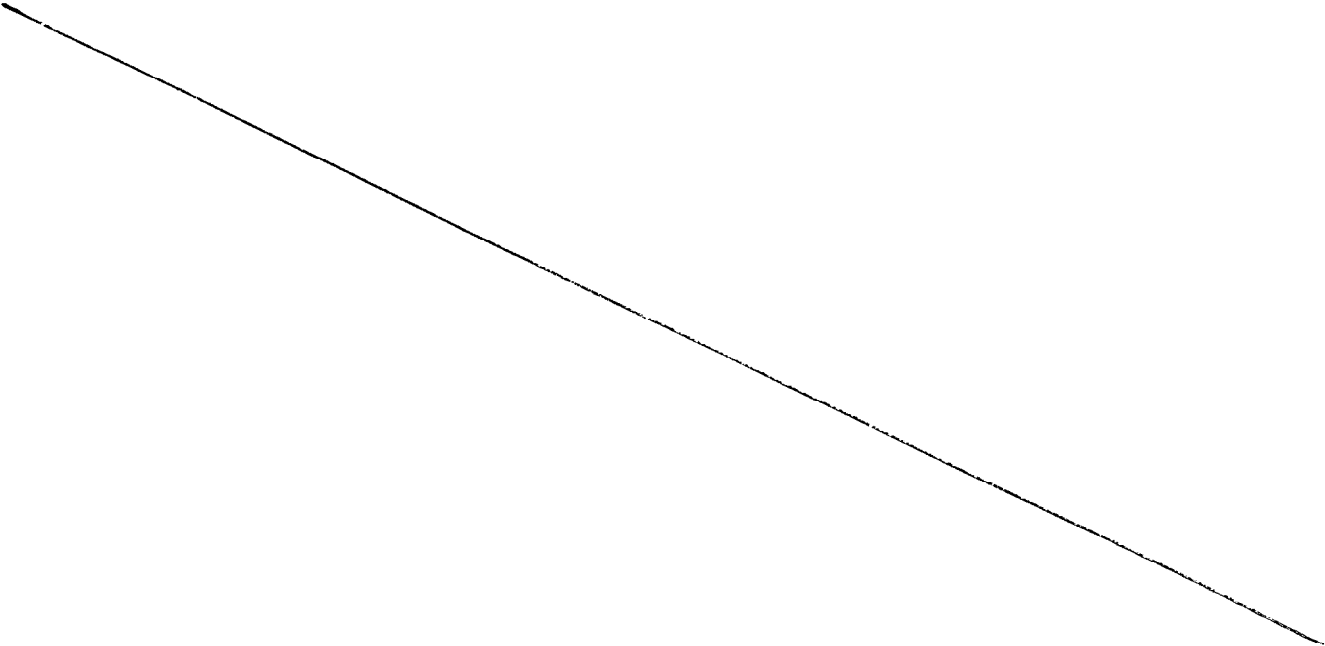
**Authority:** 21 U.S.C. 321, 342, 348, 379e.

2. Section 178.2010 is amended in the table in paragraph (b) by alphabetically adding a new entry under the headings “Substances” and “Limitations” to read as follows:

#### **§ 178.2010     Antioxidants and/or stabilizers for polymers.**

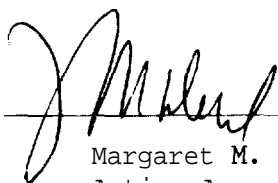
\*       \*       \*       \*       \*

(b) \* \* \*



Substances	Limitations
<p>7-Oxa-3,20-diazadispiro-[5.1.1.2]-heneicosan-21-one,2,2,4,4-tetramethyl-,hydrochloride, reaction products with epichlorohydrin, hydrolyzed, polymerized (CAS Reg. No. 202483-55-4).</p>	<p>For use only:</p> <ol style="list-style-type: none"> <li>1. At levels not to exceed 0.5 percent by weight of olefin polymers complying with § 177.1520 of this chapter, items 1.1, 3.1, and 3.2, where the copolymers complying with items 3.1 and 3.2 contain not less than 85 weight percent of polymer units derived from propylene; in contact with all types of food described in Table 1 of § 176.170 of this chapter, provided that the finished food-contact article will have a capacity of at least 18.9 liters (5 gallons) when in contact with food of types III, IV-A, V, VII-A, and IX, described in Table 1 of § 176.170 of this chapter.</li> <li>2. At levels not to exceed 0.5 percent by weight of olefin polymers complying with § 177.1520 of this chapter, items 2.1, 2.2, 3.1, and 3.2, having a density of not less than 0.94 gram/milliliter, where the copolymers complying with items 3.1 and 3.2 contain not less than 85 weight percent of polymer units derived from ethylene; in contact with food only under conditions of use C, D, E, F, and G, described in Table 2 of § 176.170 of this chapter, provided that the finished food-contact article will have a capacity of at least 18.9 liters (5 gallons) when in contact with food of types III, IV-A, V, VII-A, and IX, described in Table 1 of § 176.170 of this chapter.</li> <li>3. At levels not to exceed 0.3 percent by weight of olefin polymers complying with § 177.1520 of this chapter, items 2.1, 2.2, 3.1, 3.2, 3.3, 3.4, 3.5, 3.6, and 4.0, having a density of less than 0.94 gram/milliliter, in contact with food only under conditions of use D, E, F, and G, described in Table 2 of § 176.170 of this chapter, provided that the finished food-contact article will have a capacity of at least 18.9 liters (5 gallons) except that, films and molded articles containing not more than 0.2 percent by weight of the stabilizer may contact aqueous food of types I, II, IV-B, VI, and VIII, described in Table 1 of § 176.170 of this chapter with no restrictions on the amount of food contacted.</li> </ol>

Dated: 11-23-99  
November 23, 1999

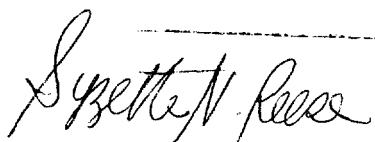


Margaret M. Dotzel  
Acting Associate Commissioner for Policy

[FR Doc. 99-???? Filed '??-??-99; 8:45 am]

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**CERTIFIED TO BE A TRUE COPY OF THE ORIGINAL**



Tab A

99F-0150

BR/610

[Federal Register: July 12, 1995 (Volume 60, Number 133)]

[Notices]

[Page 35914-35915]

From the Federal Register Online via GPO Access [[wais.access.gpo.gov](http://wais.access.gpo.gov)]

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

[Docket No. 95F-0150]

Hoechst Aktiengesellschaft; Filing of Food Additive Petition

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

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SUMMARY: The Food and Drug Administration (FDA) is announcing that Hoechst Aktiengesellschaft has filed a petition proposing that the food additive regulations be amended to provide for the safe use of polymeric 2,2,4,4-tetramethyl-7-oxa-3,20-diaza-20-(2,3-epoxypropyl)-dispiro-[5.1.11.2]-heneicosane-2 1 -one as an antioxidant and/or stabilizer for polyolefins intended for contact with food.

DATES: Written comments on the petitioner's environmental assessment by August 11, 1995.

ADDRESSES: Submit written comments to the Dockets Management Branch (HFA-305), Food and Drug Administration, rm. 1-23, 12420 Parklawn Dr., Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: Daniel N. Harrison, Center for Food Safety and Applied Nutrition (HFS-216), Food and Drug Administration, 200 C St. SW., Washington, DC 20204-0002, 202-418-3080.

SUPPLEMENTARY INFORMATION: Under the Federal Food, Drug, and Cosmetic Act (sec. 409(b)(5) (21 U.S.C. 348(b)(5))), notice is given that a food additive petition (FAP 5B4461) has been filed by Hoechst Aktiengesellschaft, c/o 1001 G St. NW., suite 500 West, Washington, DC 20001. The petition proposes to amend the food additive regulations in

Sec. 178.2010 Antioxidants and/or stabilizers for polymers (21 CFR 178.2010) to provide for the safe use of polymeric 2,2,4,4-tetramethyl-7-oxa-3,20-diaza-20-(2,3-epoxypropyl)-dispiro-[5.1.1.1.2]-heneicosane-21-one (CAS Reg. No. 78301-43-6) as an antioxidant and/or stabilizer for polyolefins intended for contact with food.

The potential environmental impact of this action is being reviewed. To encourage public participation consistent with regulations promulgated under the National Environmental Policy Act (40 CFR 1501.4(b)), the agency is placing the environmental assessment submitted with the petition that is the subject of this notice on public display at the Dockets Management Branch (address above) for public review and comment. Interested persons may, on or before August 11, 1995, submit to the Dockets Management Branch (address above) written comments. Two copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday. FDA will also place on public display any amendments to, or comments on, the petitioner's environmental assessment without further announcement in the Federal Register. If, based on its review, the agency finds that an environmental impact statement is not required and this petition results in a regulation, the

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notice of availability of the agency's finding of no significant impact and the evidence supporting that finding will be published with the regulation in the Federal Register in accordance with 21 CFR 25.40(c).

Dated: June 23, 1995.

Alan M. Rulis,

Acting Director, Office of Premarket Approval, Center for Food Safety  
and Applied Nutrition.

[FR Doc. 95-17093 Filed 7-11-95; 8:45 am]

BILLING CODE 4160-01-F

Tab B